

## Influence of Age at Menarche on Forearm Bone Microstructure in Healthy Young Women

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**Background:** Shorter estrogen exposure from puberty onset to peak bone mass attainment may explain how late menarche is a risk factor for osteoporosis. The influence of menarcheal age (MENA) on peak bone mass, cortical, and trabecular microstructure was studied in 124 healthy women aged  $20.4 \pm 0.6$  (sd) yr.

**Methods:** At distal radius, areal bone mineral density (aBMD) was measured by dual-energy x-ray absorptiometry, and volumetric bone mineral density (BMD) and microstructure were measured by high-resolution peripheral computerized tomography, including: total, cortical, and trabecular volumetric BMD and fraction; trabecular number, thickness, and spacing; cortical thickness (CTh); and cross-sectional area (CSA).

**Results:** Median MENA was 12.9 yr. Mean aBMD T score of the whole cohort was slightly positive. aBMD was inversely correlated to MENA for total radius ( $R = -0.21$ ;  $P = 0.018$ ), diaphysis ( $R = -0.18$ ;  $P = 0.043$ ), and metaphysis ( $R = -0.19$ ;  $P = 0.031$ ). Subjects with MENA more than the median [LATER:  $14.0 \pm 0.7$  ( $\pm$ sd) yr] had lower aBMD than those with MENA less than the median (EARLIER:  $12.1 \pm 0.7$  yr) in total radius ( $P = 0.026$ ), diaphysis ( $P = 0.042$ ), and metaphysis ( $P = 0.046$ ). LATER vs. EARLIER displayed lower total volumetric BMD ( $315 \pm 54$  vs.  $341 \pm 56$  mg HA/cm<sup>3</sup>;  $P = 0.010$ ), cortical volumetric BMD ( $874 \pm 49$  vs.  $901 \pm 44$  mg HA/cm<sup>3</sup>;  $P = 0.003$ ), and CTh ( $774 \pm 170$  vs.  $849 \pm 191$   $\mu$ m;  $P = 0.023$ ). CTh was inversely related to CSA ( $R = -0.46$ ;  $P < 0.001$ ). In LATER reduced CTh was associated with 5% increased CSA.

**Conclusions:** In healthy young adult women, a 1.9-yr difference in mean MENA was associated with lower radial aBMD T score, lower CTh without reduced CSA, a finding compatible with less endocortical accrual. It may explain how late menarche is a risk factor for forearm osteoporosis. (*J Clin Endocrinol Metab* 93: 2594–2601, 2008)

The notion that pubertal timing is related to the risk of osteoporosis during adult life has been so far primarily documented in female subjects. In postmenopausal women, later age at menarche was found to be associated with lower areal bone mineral density (aBMD) in the spine, radius, and proximal femur (1–4). It was also associated with higher risk of hip (5, 6), vertebral (7), and forearm fractures (8). In premenopausal women early menarche is associated with higher aBMD (9–11).

Retrospective epidemiological surveys in premenopausal women provide indirect evidence that the association between

menarcheal age (MENA) and osteoporosis risk may be related to the influence of pubertal timing on the attainment of peak bone mass (PBM). This association is usually considered as the expression of variation in the duration of exposure to estrogen (12–14).

The risk of fragility fracture is dependent upon the mass of mineralized tissue, its distribution within the bone, as well as of several microstructural components. In women a large portion of these different bone components that play a role in determining the mechanical resistance to loading is acquired by the end of the

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Abbreviations: aBMD, Areal bone mineral density; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; BV/TV, trabecular bone volume fraction; BW, body weight; CSA, cross-sectional area; CTh, cortical thickness; CV, coefficient of variation; Dcort, cortical volumetric bone density; Dtort, total volumetric bone density; Dtrab, trabecular volumetric bone density; DXA, dual-energy x-ray absorptiometry; HR-pQCT, high-resolution peripheral computerized tomography; MENA, menarcheal age; PBM, peak bone mass; TbN, trabecular number; TbSp, trabecular spacing; TbTh, trabecular thickness.

second or beginning of the third decade. During pubertal maturation, cross-sectional analysis of appendicular bone, at least in the upper limb, reveals distinct gender dimorphisms. In contrast to characteristics of male skeletal development during puberty, bone mineral mass in females increases more by endocortical than periosteal accrual (15–17). This increase in endocortical deposition is considered as a specific feature of estrogen exposure. Therefore, it is possible that the increased risk of fragility fractures observed in postmenopausal women with later menarche (5–8) would be related, at least in part, to the influence of reduced estrogen exposure between the onset of pubertal maturation and the end of bone mass acquisition on the process of endosteal accrual. This would result in diminished cortical thickness (CTh) without reduction or even with an increase in cross-sectional area (CSA).

In the present investigation, we tested this hypothesis in a cohort of healthy female subjects followed from age 8–20 yr, during which time MENA was prospectively recorded.

## Subjects and Methods

### Participants

We studied 124 healthy women with a mean ( $\pm$  SD) age of  $20.4 \pm 0.6$  yr. They belong to a cohort followed during 12 yr and previously examined at mean age 7.9, 8.9, 9.9 (18), 12.5 (19), and 16.4 yr (20). During 1 yr, between 7.9 and 8.9 yr of age, half the cohort received a supplementation of calcium in a randomized, double-blind, placebo-controlled design as previously reported (18). The ethics committee of the Department of Pediatrics of the University Hospitals of Geneva approved the protocol while informed consent was obtained from both parents and children. All subjects were recruited within the Geneva district.

### Clinical assessment

Weight, standing height, and body mass index (BMI) ( $\text{kg}/\text{m}^2$ ) were measured. At the first examination when aged  $7.9 \pm 0.5$  (SD) yr, all of them were prepubertal (stage P1) as assessed by a pediatrician-endocrinologist (18). The exclusion criteria were weight to height ratio less than the 3rd or more than the 97th percentile, physical signs of puberty, chronic disease, malabsorption, bone disease, and regular use of medication. MENA was then assessed prospectively by direct interview at the second, third, fourth, and fifth visits, *i.e.* at the mean age of 8.9, 9.9, 12.5, and 16.4 yr.

### Assessment of calcium and protein intakes, and physical activity

Calcium and protein intakes were assessed by a frequency questionnaire (21, 22). The calcium intake was essentially recorded from dairy sources (21). The total protein intake was expressed either in  $\text{g}/\text{d}^{-1}$  or  $\text{g}/\text{kg}$  body weight (BW)  $\cdot \text{d}^{-1}$ . It included dairy, meat, fish, and egg proteins (22).

Physical activity was assessed by a questionnaire based on self-reported time spent on physical education classes, organized sports, recreational activity, usual walking, and cycling (23). Subsequently, the collected data were converted and expressed as physical activity energy expenditure ( $\text{kcal}/\text{d}^{-1}$ ) using an established conversion formula (24).

### Bone variables

Volumetric bone density and microstructure were determined at the distal radius by high-resolution peripheral computerized tomography (HR-pQCT) on an XtremeCT instrument (Scanco Medical AG, Brütisellen, Switzerland) that acquires a stack of 110 parallel computerized

tomography slices (9-mm length) with an isotropic voxel size of  $82 \mu\text{m}$ , as previously described (25). The site of the HR-pQCT scan was precisely delineated by positioning a reference line at the endplate of the radius. The first computerized tomography slice was 9.5-mm proximal to the reference line. The following variables were measured: total (Dtot), cortical (Dcort), and trabecular (Dtrab) volumetric bone density ( $\text{g}$  hydroxyapatite per  $\text{cm}^3$ ); trabecular bone volume fraction (BV/TV) (%); trabecular number (TbN) ( $\text{mm}^{-1}$ ), thickness (TbTh) ( $\mu\text{m}$ ), and spacing (TbSp) ( $\mu\text{m}$ ); and mean CTh ( $\mu\text{m}$ ) and CSA ( $\text{mm}^2$ ). The short-term reproducibility of HR-pQCT at the distal radius varied from 0.6–1.0% and from 2.8–4.9% for bone density and trabecular architecture, respectively. To compare these cortical and trabecular microstructure variables recorded at this skeletal site, aBMD ( $\text{mg}/\text{cm}^2$ ) and content (BMC) (mg) were determined in the radius (total, metaphysis, and diaphysis) by dual-energy x-ray absorptiometry (DXA) on a Hologic QDR-4500 instrument (Hologic, Inc., Bedford, MA) as previously reported (20). The coefficient of variation (CV) of repeated aBMD measurements as determined in young healthy adults varied between 1.0 and 1.6%.

### Expression of the results and statistical analysis

The various anthropometric and osteodensitometric variables are given as mean  $\pm$  SD. The T score based on the reference range provided by the DXA manufacturer was used to assess whether the cohort mean value with a 95% confidence interval of radial aBMD could be considered as being at PBM. For all measured bone variables, the CVs were calculated as:  $\text{CV} = (\text{SD}/\text{mean}) \times 100$ . Pearson's correlation coefficients  $R$  were calculated for the relationships between aBMD and BMC of the radial metaphysis as determined by DXA, and bone structural elements of the distal radius as measured by HR-pQCT. The relationships between MENA and bone variables were examined by univariate and multiple regression analysis to adjust for calcium intervention, standing height, and BW. The cohort was also segregated according to the median of MENA. Menarche under and above the median age of the first menstruation occurrence was defined as “EARLIER” and “LATER,” respectively. To compare on an identical quantitative scale the differences in DXA and HR-pQCT bone variables between the EARLIER and LATER groups, the microstructural components of the distal radius were also expressed in SD scores. These so designated “T” scores were calculated from an external cohort of healthy 34-yr-old French (25) women who were recently measured on the same HR-pQCT model as the one used in the present study. The statistical significance of the differences between relatively EARLIER and LATER MENA groups was evaluated by a two-tailed  $t$  test for unpaired values or by the Wilcoxon rank sum test whenever some degree of skewed distribution was present for either one compared bone variable. The significance level for two-sided  $P$  values was 0.05 for all tests. The data were analyzed using STATA software, version 7.0 (StataCorp LP, College Station, TX).

## Results

### Demographical characteristics

Both anthropometric and MENA variables were well within reference values previously recorded in similar ethnic and socioeconomic populations (26–29) (Table 1). The calcium and protein intakes as assessed by a food frequency questionnaire corresponded to about 80–90% of the usual dietary allowance for young adult women as recommended in several countries (calcium intake:  $1000 \text{ mg}/\text{d}^{-1}$ ; protein intake  $0.8 \text{ g}/\text{kg}$  BW  $\cdot \text{d}^{-1}$ ) (30–34).

### DXA measurements

The mean aBMD T scores of the three DXA scanned regions of the radius were slightly positive as computed according to the

**TABLE 1.** Characteristics of the 124 young adult women

Age (yr)	20.4 ± 0.6
Height (cm)	165.0 ± 6.0
Weight (kg)	60.0 ± 9.2
BMI (kg/m <sup>2</sup> )	22.1 ± 3.4
MENA (yr)	13.0 ± 1.2
Calcium intake (mg/d <sup>-1</sup> )	832 ± 380
Protein intake (g/d <sup>-1</sup> )	41.6 ± 16.7
Protein intake (g/kg BW·d <sup>-1</sup> )	0.71 ± 0.31
Physical activity (kcal/d <sup>-1</sup> )	352 ± 298

All values are means ± SD.

reference range used in the clinical unit that is dedicated to the diagnosis of osteoporosis (Table 2).

### HR-pQCT measurements

The mean values (±SD) of the structural components of distal radius (Table 3) were very close to those reported for a group of healthy women with mean age 34 ± 7 yr (25). The CVs [CV = (SD/mean) × 100] ranged from 5.4% for Dcort to 22.7% for CTh (Table 3). They were also quite large for both CSA (CV = 17.2%) and Dtrab or BV/TV (CV = 20.4 or 20.0%). The CV for radial metaphysis aBMD was 11.3% (Table 2). For comparison it was only 3.6% for standing height (Table 1).

The correlation coefficient with aBMD of the distal metaphysis as assessed by DXA was the highest with Dtrab (or BV/TV): R = 0.73, P < 0.001 (Table 3). The degree of correlation was also statistically significant between aBMD and Dcort or CTh but somewhat less than with Dtrab.

Among the microstructural components, CSA was inversely correlated with CTh (R = -0.46; P < 0.001) (Fig. 1), but not with Dtrab, or BV/TV (R = 0.03). Dcort was not correlated with Dtrab or BV/TV (R = 0.02).

### Influence of MENA

After segregation of the cohort according to the median of MENA, only a 1.9-yr difference (12.1 vs. 14.0 yr) separated the two groups with similar variability around mean MENA (SD = 0.7 yr) (Table 4). At examination time, there was no difference in age, standing height, calcium and protein intakes, and physical activity. The only significant difference between the two groups was the BMI, which was lower by 5%, in the LATER compared with the EARLIER menarcheal group. This difference in BMI was essentially due to a lower BW in the LATER subjects (Table 4).

The values of aBMD were inversely related to MENA in total radius (R = -0.21; P = 0.018), and at both diaphyseal (R = -0.18; P = 0.043) and metaphyseal (R = -0.19; P = 0.031) sites (Fig. 2A). As detailed in the legend to Fig. 2A, the statistical

**TABLE 2.** Absolute and T-score values of radial aBMD of the 124 young adult women

Skeletal site	aBMD (mg/cm <sup>2</sup> ± SD)	T score (95% CI)
Total radius	594 ± 44	+0.28 (+0.06 to +0.46)
Radial diaphysis	710 ± 50	+0.27 (+0.10 to +0.46)
Radial metaphysis	452 ± 51	+0.16 (-0.06 to +0.24)

T scores are expressed as means with 95% confidence intervals (CIs). See *Subjects and Methods* for further details.

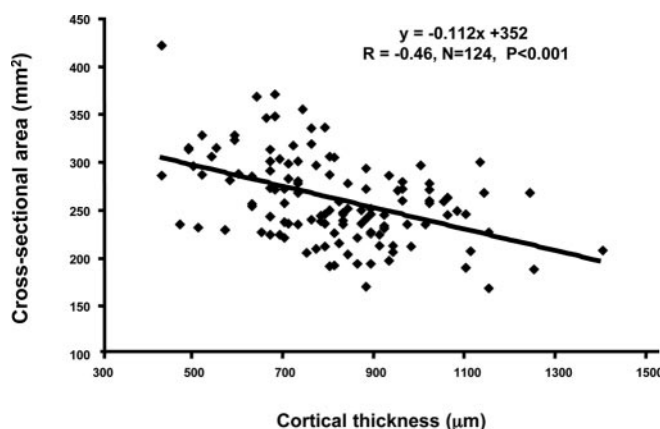
**TABLE 3.** Values of bone structural elements of distal radius as measured by HR-pQCT

	Mean ± SD	Correlation (R) with radial metaphysis	
		aBMD	BMC
Dtot (mg HA/cm <sup>3</sup> )	328 ± 57	0.70	0.34
P value		<0.001	<0.001
Dcort (mg HA/cm <sup>3</sup> )	887 ± 48	0.37	0.13
P value		<0.001	0.155
Dtrab (mg HA/cm <sup>3</sup> )	162 ± 33	0.73	0.47
P value		<0.001	<0.001
BV/TV (%)	13.5 ± 2.7	0.73	0.47
P value		<0.001	<0.001
TbN (mm <sup>-1</sup> )	1.99 ± 0.25	0.43	0.33
P value		<0.001	<0.001
TbTh (μm)	68 ± 10	0.65	0.37
P value		<0.001	<0.001
TbSp (μm)	443 ± 66	-0.49	-0.38
P value		<0.001	<0.001
CTh (μm)	811 ± 184	0.57	0.32
P value		<0.001	<0.001
CSA (mm <sup>2</sup> )	261 ± 45	0.02	0.47
P value		0.47	<0.001

Correlation with aBMD and BMC as determined by DXA at the radial metaphysis in 124 healthy young adult women.

significance of these three relationships between DXA measured aBMD and MENA were greater than the 0.05 level after adjustment for calcium intervention, standing height, and BW. After segregation by the median of MENA, the aBMD T score was significantly lower in the LATER vs. EARLIER group for total radius (P = 0.026), radial diaphysis (P = 0.042), and metaphysis (P = 0.046) (Fig. 2B). The corresponding absolute aBMD and BMC values are given in Table 5.

The values of total density (R = -0.23; P = 0.011), cortical density (R = -0.27; P = 0.002), and CTh (R = -0.16; P = 0.085) of the distal radius were inversely related to MENA (Fig.



**FIG. 1.** Relationship between CSA and CTh at the distal radius in healthy young adult women. The equation of the regression line is indicated above the scatterplot. The inverse relationship is compatible with the concept that thinner cortex is associated with greater periosteal apposition, thus compensating, at least partially, for the diminished mechanical resistance to bending and torsional loadings resulting from the reduced amount of bone material. Inverse correlations between CSA and CTh were also present in both EARLIER (R = -0.46; P < 0.001; n = 62) and LATER (R = -0.44; P < 0.001; n = 62) menarcheal groups.

**TABLE 4.** Characteristics of healthy young adult women segregated by the median of MENA

	EARLIER (n = 62)	LATER (n = 62)
MENA (yr)	12.1 ± 0.7	14.0 ± 0.7
Age (yr)	20.4 ± 0.6	20.4 ± 0.6
Height (cm)	164.7 ± 6.1	165.1 ± 6.3
Weight (kg)	61.4 ± 8.7	58.5 ± 9.6 <sup>a</sup>
BMI (kg/m <sup>2</sup> )	22.7 ± 3.3	21.5 ± 3.4 <sup>b</sup>
Calcium intake (mg/d)	836 ± 368	827 ± 394
Protein intake (g/d)	42.1 ± 15.0	41.1 ± 18.4
Protein intake (g/kg BW·d <sup>-1</sup> )	0.70 ± 0.28	0.72 ± 0.35
Physical activity (kcal/d)	344 ± 335	360 ± 259

All values are means ± sd. The median of the MENA of the 124 subjects was 12.94 yr.

<sup>a</sup> *P* = 0.061 using the Wilcoxon rank sum test for skewed distribution.

<sup>b</sup> *P* = 0.022 using the Wilcoxon rank sum test for skewed distribution.

3A). As detailed in the legend to Fig. 3A, the statistical significance of the relationships between MENA and HR-pQCT measured total radius density and cortical density remained below the 0.05 level after adjustment for calcium intervention, standing height, and BW.

After segregation by the median of MENA, the “T” score was significantly lower in the LATER *vs.* EARLIER group for total density (*P* = 0.010), cortical density (*P* = 0.003), and CTh (*P* = 0.023) (Fig. 3B). The corresponding absolute values of these three variables as well as other measured microstructural components are given in Table 6. The lower total density, cortical density, and CTh observed in the LATER group remained statistically significant after adjustment for calcium intervention, standing height, and BW. Of note, the 8.8% reduction of CTh in the LATER group was not associated with a decrease, but rather with a 5% increase in CSA. This difference became statistically significant after adjustment for calcium intervention, standing height, and BW (*P* = 0.026) (Table 6). In contrast to the significant relation between MENA and cortical variables as measured by HR-pQCT, no difference was found between the EARLIER and LATER groups for the trabecular microstructure components, Dtrab, or BV/TV, TbN, TbTh, and TbSp.

## Discussion

### Influence of MENA on microstructure and bone mass distribution

In this cohort MENA was prospectively recorded since prepuberty. The inverse relationship between the occurrence of the first menstruation and peak aBMD was observed in the three DXA scanned regions of the radius (Fig. 2A). The analysis according to the median of MENA indicates that a 2-yr difference in this signal of the onset of reproductive life (12.1 *vs.* 14.0 yr), within the normal range, *i.e.* in the absence of abnormal precocious or delayed sexual maturation, showed a substantial difference in radial aBMD. When expressed in T score, the later menarche age group displayed a deficit by about 0.4 sd. Considering that a deficit of 1.0 sd would double the risk of fracture,

the 2-yr difference in MENA observed in our cohort may increase the relative risk of fragility fracture by up to 40%.

At the microstructural level, the inverse relationship with MENA was particularly noticed at the level of the cortical density and thickness. There was also a trend for a larger CSA in the LATER menarcheal group. As expressed in “T” score, the deficit in the LATER group was still greater than that observed by DXA on aBMD. The deficit was particularly sustained in cortical density (−0.60 sd) and CTh (−0.45 sd). This would corroborate previous observations in postmenopausal women (35) suggesting that the sensitivity for detecting differences in bone fragility would be greater by using HR-pQCT than DXA, at least for measurements made at the level of the distal radius.

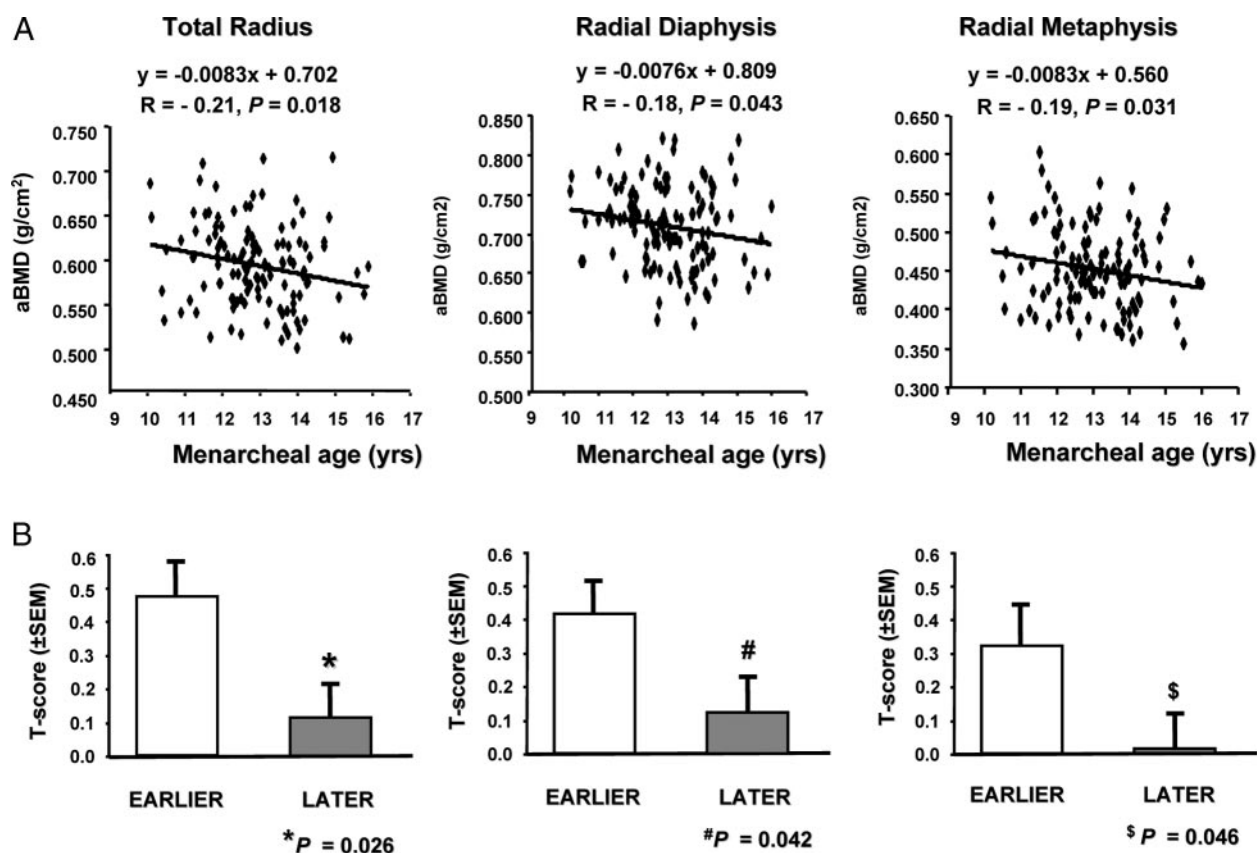
During pubertal maturation cross-sectional analysis of appendicular bone, at least in the upper limb, reveals a distinct gender dimorphism. In female subjects bone mineral mass increases more by endosteal than periosteal deposition (15). This endosteal deposition appears to be an estrogen-dependent phenomenon (16, 17, 36). The results of our study obtained in healthy women in their early 20s suggest that within the physiological range of pubertal maturation, a 2-yr delay in MENA (LATER: 6.4 yr; EARLIER: 8.3 yr) would tend to reduce CTh by shortening the exposure time to estrogen and thereby reducing endosteal deposition. As discussed previously, this negative impact on CTh would tend to be partially compensated in terms of mechanical resistance by more external distribution of the reduced bone mass. It remains that this compensation may well be insufficient with the additional postmenopausal bone loss for negating the risk of fracture. Indeed, it has been well documented that in postmenopausal women, late menarche is associated with low aBMD (1–4) and a higher risk of fragility fractures at several skeletal sites, including at the forearm level (5–8).

Our data suggest that apparent shorter exposure to estrogen during bone acquisition would affect cortical but not trabecular constituents of the distal radius. This contrasts with the marked detrimental effect of estrogen deficiency on trabecular structure observed in adulthood by comparing HR-pQCT values of the distal radius in premenopausal and postmenopausal women (25). As suggested in a recent review (37), it is possible that the association of MENA with bone acquired in early adulthood is not the mere result of variation in the duration of estrogen exposure. Pubertal timing and bone mass acquisition may be part of a common programming in which both genetic and *in utero* influences are important determinants (37).

BMI is a well-documented risk factor for osteoporosis (38, 39). The 5% BW deficit in the LATER compared with the EARLIER menarche group may have contributed by some still unidentified mechanism(s) to the onset of pubertal timing and the relatively low bone variables as recently reviewed (37). In our study the fact that the statistical significance of the differences between LATER and EARLIER subjects for Dtot, Dcort, and CTh was maintained after adjustment for BW suggests that the influence of MENA is not entirely dependent upon some pathophysiological pathway involving variations in body mass (40).

As a limitation to the interpretation of the presented data, it may be argued that the MENA-related differences in aBMD, and cortical density and thickness as determined at the distal radius





**FIG. 2.** Influence of MENA on aBMD of the radius in healthy young adult women. A, MENA was inversely related to aBMD in total radius and at both diaphyseal and metaphyseal sites ( $n = 124$ ). Linear equations with  $P$  values without adjustment are indicated above the three scatterplots.  $P$  values after adjustment for calcium intervention, standing height, and BW were 0.069, 0.110, and 0.117 for total radius, radial diaphysis, and radial metaphysis, respectively. B, The cohort of the 124 healthy women was segregated by the median of MENA. aBMD T score was significantly lower in the LATER ( $n = 62$ ) vs. EARLIER ( $n = 62$ ) group for total radius, radial diaphysis, and metaphysis. The corresponding absolute aBMD and BMC values are presented in Table 5. See Results section for further details.

by DXA and HR-pQCT might only be a transient phenomenon. Indeed, no absolute proof can be provided that PBM of distal radius was actually attained at examination in this cohort of healthy women in their very early 20s. It can be inferred that the inverse relationship between MENA and aBMD, and cortical density and thickness might no longer be present a few years later when the percent difference in the duration of estrogen exposure would be attenuated. In other words, we cannot exclude that

radial PBM would be attained at a more advanced age in women whose pubertal maturation was relatively delayed. Nevertheless, there is indirect support in our interpretation suggesting that late pubertal timing is associated with low PBM. Indeed, numerous studies have documented that late MENA is associated with low bone mineral density (BMD) in both premenopausal and postmenopausal women and increased risk of fragility fractures in late adulthood (1–14).

**TABLE 5.** Radial BMC and aBMD values of healthy young adult women according to the median of MENA

	EARLIER ( $n = 62$ )	LATER ( $n = 62$ )
Total radius BMC	$7903 \pm 1713$	$7425 \pm 1203$
Total radius aBMD	$604 \pm 45$	$585 \pm 47^a$
Radial diaphysis BMC	$1971 \pm 450$	$1851 \pm 275$
Radial diaphysis aBMD	$720 \pm 46$	$701 \pm 53^b$
Radial metaphysis BMC	$1596 \pm 268$	$1515 \pm 237$
Radial metaphysis aBMD	$462 \pm 53$	$443 \pm 48^c$

Values are means  $\pm$  SD in mg and mg/cm<sup>2</sup> for BMC and aBMD, respectively.

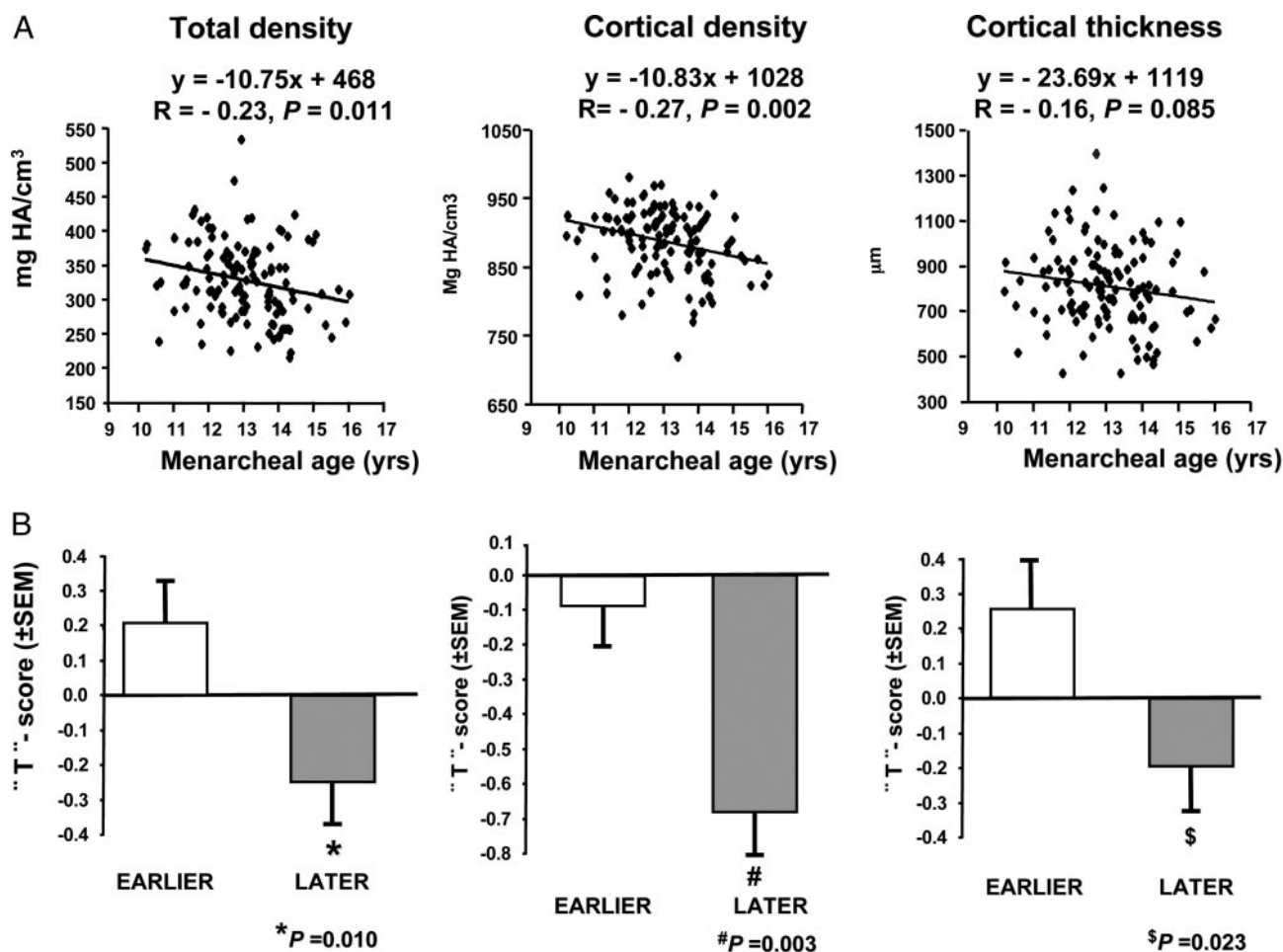
<sup>a</sup>  $P = 0.026$  for differences between the EARLIER and LATER MENA groups by the Student's  $t$  test.

<sup>b</sup>  $P = 0.042$  for differences between the EARLIER and LATER MENA groups by the Student's  $t$  test.

<sup>c</sup>  $P = 0.046$  for differences between the EARLIER and LATER MENA groups by the Student's  $t$  test.

### CTh and CSA

The CSA was inversely correlated to the CTh. This suggests some adaptation because a more outward distribution of the bone mineral mass would tend to compensate for cortical thinning according to an important concept of biomechanical resistance (41). A small increase in the external diameter of appendicular bones can markedly improve the resistance to bending and torsional loadings (41–43). The moment of inertia or the resistance to bending and torsional loads, the highest mode of stresses in the appendicular skeleton, is markedly influenced by the distribution of the bone mineral mass away from the neutral axis, *i.e.* from the center of the bone. Such an apparently adaptive redistribution of bone mass was described in relation with aging several decades ago (44, 45). The age-related decrease in CTh probably results from increased endosteal resorption, which is



**FIG. 3.** Influence of MENA on bone microstructure of the radius in healthy young adult women. **A**, MENA was inversely related to total density, cortical density, and CTh of the distal radius ( $n = 124$ ). Linear equations and  $P$  values are indicated above the scatterplots.  $P$  values after adjustment for calcium intervention, standing height, and BW were 0.018, 0.002, and 0.091 for total density, cortical density, and CTh, respectively. **B**, The cohort of the 124 healthy women was segregated by the median of MENA. The “T” score calculated from an external cohort of healthy French women with a mean age of  $34 \pm 7$  yr (25) was significantly lower in the LATER ( $n = 62$ ) vs. EARLIER ( $n = 62$ ) group for total density, cortical density, and CTh of the distal radius. The corresponding absolute values are given in Table 6, which also includes other measured microstructural components. See *Results* section for further details.

accompanied by an increase in periosteal apposition, leading to an increase in the outer diameter of appendicular bones, and thereby attenuating the loss in resistance to bending and torsional loadings (41).

In the present work in young healthy adult women, the observed inverse relationship between CTh and CSA at the level of the radial metaphysis might be due to an adaptation to mechanical stress during growth. Alternatively, it may be the expression of an evolutionary phenomenon that would be genetically determined. The presence in very early infancy of such an inverse relationship between CTh and CSA would favor a genetically determined trait that would compensate by shifting a relatively low bone mass away from the neutral axis. This concept has been recently presented for the construction of the femoral neck during growth in relation with its strength in old age (46). It was proposed that greater periosteal apposition constructing a wider femoral neck was offset by even greater endocortical resorption so that the same net amount of bone would be distributed as a thinner cortex further from the neutral axis, increasing the resistance to bending and lowering volumetric BMD. The redistribution of bone mass according to the amount of available

material appears to be observed not only in classically weight-bearing bone such as femoral neck and diaphysis (41, 44–46), but also, as shown in the current study, in the distal forearm. Our observation would suggest that this phenomenon is not essentially dependent upon mechanical forces undergone during growth.

#### Physiological variability of microstructural components in healthy young adults

The use of HR-pQCT allows one to get insight into the microstructural components of appendicular bones. In the present study performed in healthy young adult females having attained PBM, the CVs differed markedly from one component to the other. Thus, in the cortical compartment of the distal metaphysis of the radius, the variability of the thickness was about 4.2 times larger than that of the volumetric mineral density (22.8 vs. 5.4%). This strongly suggests that the biological variability of the cortical structure is much more due to a difference in size than in the amount of mineral per volume unit of cortical bony tissue. In agreement with the importance of bone size, the interindividual variability of the CSA of the distal radius was also quite large,

**TABLE 6.** Bone structure of distal radius in healthy young adult women according to the median of MENA

	EARLIER (n = 62)	LATER (n = 62)
Dtot (mg HA/cm <sup>3</sup> )	341 ± 56	315 ± 54 <sup>a</sup>
Dcort (mg HA/cm <sup>3</sup> )	901 ± 44	874 ± 49 <sup>b</sup>
Dtrab (mg HA/cm <sup>3</sup> )	166 ± 32	158 ± 34
BV/TV (%)	13.8 ± 2.7	13.2 ± 2.8
TbN (mm <sup>-1</sup> )	2.01 ± 0.25	1.96 ± 0.24
TbTh (μm)	69 ± 9	67 ± 11
TbSp (μm)	436 ± 65	450 ± 66
CTh (μm)	849 ± 191	774 ± 170 <sup>c</sup>
CSA (mm <sup>2</sup> )	255 ± 40	268 ± 49

Values are means ± SD.

<sup>a</sup> *P* = 0.010 by the Wilcoxon rank sum test for differences between the EARLIER and LATER menarche groups.

<sup>b</sup> *P* = 0.003 by the Wilcoxon rank sum test for differences between the EARLIER and LATER menarche groups.

<sup>c</sup> *P* = 0.023 by the Student's *t* test for differences between the EARLIER and LATER menarche groups.

with a CV amounting to 17.2%. In the trabecular compartment, the interindividual variability of the BV/TV was also quite large, suggesting that the amount of bony tissue within the bone was also an important component of the overall variance of PBM at this skeletal site because it can be assessed by DXA in measuring aBMD (CV = 11.3%) or BMC (CV = 16.4%). As previously observed in the lumbar spine of healthy young adults (47), the CV for aBMD or BMC was much larger than that of standing height, which in the present cohort, was only 3.6%. This emphasizes again the importance of PBM in the individual risk of fragility fractures that can occur during the second half of adult life. It also underscores the notion that PBM is largely independent of standing height (47).

The quantitative analysis of the relationships between microstructural variables indicates that the estimates of volumetric density of the trabecular compartment were not at all correlated with that of the cortical compartment. This absence of association suggests for these two components of PBM and strength the influential role of distinct determinants, whether of genetic and/or environmental nature.

In conclusion, in healthy young adult women, a 2-yr later occurrence in the mean age of menarche within the normal range was associated with lower radial aBMD. Furthermore, in the LATER menarcheal group, CTh of the distal radius was decreased and was associated with a small increase in the external perimeter of the metaphysis. This finding would be compatible with less endocortical bone accrual. Our study suggests that estrogen exposure from the onset of sexual maturation to the end of growth influences PBM with modifications of several microstructural components. A deficit in cortical density and thickness in the distal radius may explain how late menarche is a risk factor for osteoporotic fracture at the level of the forearm.

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